Rotation Thromboelastometry (ROTEM®) as a useful tool for the intraoperative patient blood management

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„Rotation Thromboelastometry (ROTEM®) as a useful tool for the intraoperative patient blood management“

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Introduction

In the last years it has become evident that allogenic blood transfusions are associated with increased mortality, morbidity and major adverse outcomes. Reduction in the use of blood products should therefore be a main focus. Furthermore the costs of red blood cell transfusions have been largely underestimated, even when excluding the costs for treatment of adverse events and prolonged intensive care and hospital stay related to red blood cell transfusions. Therefore Patient Blood Management was adopted by the World Health Organisation (WHO) in 2010 in order to improve patient outcome. The three pillars of Patient Blood Management comprise: 1) detection and treatment of preoperative anemia, 2) reduction in perioperative blood loss and 3) harnessing and optimizing the patient specific physiological reserve of anemia (including restrictive hemoglobin transfusion triggers). The use of point of care devices such as ROTEM® (ROTEM® delta, TEM® International GmbH, Munich, Germany) to reduce the perioperative blood loss by a goal directed correction of coagulation deficiencies has become a standard operating procedure in many hospitals. This approach allows reducing the use of fresh frozen plasma, red blood cell concentrates and platelets.

Rotation thromboelastometry (ROTEM®), a methodology based on thromboelastography originally described by Hartert in 1948, is used today to rapidly assess the visco-elastic properties of the developing clot in surgery as well as following trauma. ROTEM® documents in whole blood the interaction of platelets with the coagulation factors from initial platelet—fibrin interaction, through platelet aggregation, clot strengthening and fibrin cross-linking to eventual clot lysis. Compared to standard laboratory coagulation tests which are performed in plasma only and take at least 30-45 minutes to get results ROTEM® tracing provides within 10 minutes information on clotting factor activity, platelet function, any clinically significant fibrinolysis and allows to quickly guide goal directed transfusions of coagulation factors and classical blood products such as platelets.

Research objective

Aim of the presented research on ROTEM® was to:

- validate this point of care device
- show its implication in patient blood management
- demonstrate its usefulness in the clinical setting of trauma and cardiac surgery
- discuss the interchangeability of standard laboratory test and ROTEM® in major surgery with hemorrhage
- investigate in vitro effect of factor XIII supplementation on the clot

Research summary

Validation of ROTEM® and in vitro supplementation of factor XIII

In a first study the validation on reproducibility (inter- and intra-assay variability) and sample stability over time was investigated.[1] In 48 healthy patients in eight age groups (below 20 years; 20-30 years; 30-40 years; 40-50 years; 50-60 years; 60-70 years; 70-80 years; and above 80 years), each containing three men and three women, pre-analytic aspects, blood was drawn and stored in citrated tubes at room temperature. Sample stability over time, reference intervals and effect of age and sex on ROTEM® parameters were assessed. The tests were performed every 30 min from T 0 minutes up to T 120 minutes on two identical ROTEM® devices with: INTEM (ellagic acid activated intrinsic pathway), EXTEM (tissue factor-triggered extrinsic pathway) and FIBTEM (with platelet inhibitor (cytochalasin D) evaluating the contribution of fibrinogen to clot formation). Each test was run for 60 minutes. To evaluate the precision of the devices intra- and inter-assay variability was measured in citrated blood in ten volunteers at two points of time, using the same three tests. This study was able to show that blood was stable over 120 minutes thus resulting in identical results in all tests during the entire 2h period. In addition, the variability of the tests was minimal. The maximum clot firmness (MCF) measurements had a coefficient of variation of <3% for

EXTEM, <5% for INTEM <6% for FIBTEM. The clot formation time (CFT) showed a coefficient of variation of <4% for EXTEM and <3% for INTEM, for FIBTEM this value does not have a clinical implication. Coefficient of variation for angle alpha was <3% for EXTEM and <6% for INTEM and does not exist for FIBTEM measurements. The coefficient of variation for clotting time (CT) was <15% for both EXTEM and INTEM and does not have a clinical implication for FIBTEM. A small but significant difference between ROTEM® devices was found for the MCF in FIBTEM and INTEM as well as for the CFT and alpha angle in INTEM. For INTEM these differences do not have a clinical implication. For FIBTEM this difference in MCF results has a clinical implication and may influence the administration of fibrinogen thus analysis should be performed on the same ROTEM® device if small differences are of importance for treatment. After 10 min of running time the MCF of EXTEM, INTEM and FIBTEM reached at least 98% of the final MCF value, which is an important finding as goal directed replacement of coagulation factors can be started at that moment of time. Age and gender specific changes could be found showing an increase of MCF, angle alpha and a decrease for CFT in all tests with advancing age and a greater coagulability in women.

Based on these findings a second in vitro study was performed aiming at determination of the impact of the addition of factor XIII on clot stability as assessed by ROTEM®.[2] As factor XIII is an essential parameter for final clot stability and drops quickly in many clinical situaions to critical levels its replacement and monitoring seemed essential especially if results are to be obtained faster than by laboratory determination. In this trial 90 intensive care patients were enrolled and ROTEM® measurements were performed at baseline (no addition of factor XIII), after in vitro addition of factor XIII 0.32 IU, 0.63 IU, 1.25 IU and compared to controls where only the diluent (aqua injectabile) was added. The above factor XIII addition resulted in approximate factor XIII concentrations of 150, 300 and 600%. The two tests run were EXTEM and FIBTEM and standard ROTEM® parameters (CT; CFT; MCF, angle alpha

and ML) were analyzed. Additionally, laboratory values for factor XIII, fibrinogen, platelets and hematocrit were contemporaneously determined. Fibrinogen being an acute phase protein was elevated in all patients with a mean concentration of 5.2 g/l and mean factor XIII was lowered at 62%. This phenomenon can be considered as a relative factor XIII deficiency in critically ill patients and we thus introduced a fibrinogen: factor XIII ratio. With this ratio we were able to show that supplementation of factor XIII led to a fibrinogen concentration-dependent increase in MCF and alpha angle and to a decreased CFT and ML in FIBTEM and EXTEM. These aspects showed that the addition of factor XIII increases clot firmness, accelerates clot formation and increases clot stability.

The clinical impact of ROTEM® and its use / application in special clinical settings

1) Jehovah's witnesses

As shown by the previous two studies ROTEM® is a reliable device regarding precision and reproducibility and can be used to guide goal directed transfusions regarding factor XIII.[1,2] In a third study in elective cardiac surgery with a special group of patients, namely Jehovah's witnesses, these findings were integrated and used in the second pillar of Patient Blood Management.[3] Due to their refusal of blood products perioperative anemia was diagnosed and treated with iv iron and erythropoietin to achieve normal hemoglobin levels for the day of surgery. Hemodynamic optimization was attempted by fluid resuscitation, Trendelenburg positioning and catecholamine administration. Body temperature was continuously monitored and adapted to the surgical procedure to prevent additional blood loss, hypothermia ≤ 35 °C was avoided to reduce blood loss due to hypothermia induced coagulopathy, and warming systems were used. In addition to this, the Cell Saver system was applied for continuous autotransfusion for efficient blood salvage. The only fluid received by these patients was priming solution, Ringer's Lactate and hydroxylethyl starch. Controlled hypotension was also used to reduce intraoperative blood loss. To minimize bleeding from the sternum bone wax

was used as standard in every patient. Other synthetic hemostatic agents, such as fibrin glue were administered to stop and minimize blood loss from diffuse bleeding.

The intraoperative and postoperative management consisted in maintaining a good perfusion of organs and tissues and applying Patient Blood Management. Mean arterial pressure had to be between 60 and 70 mmHg, and when needed noradrenalin, phenylephrine, dobutamine and vasopressin were used. Laboratory controls and blood drawn was reduced to a minimum. Coagulation was controlled by laboratory values as well as by ROTEM® and substitution of fibrinogen and coagulation factors were substituted according to institutional guidelines and ROTEM® results.

Male gender was predominant (64%), mean age was 63±17 years, preoperative EuroSCORE was 5.7±1.9, the mean preoperative ejection fraction 65±7%, mean body mass index 28±6 and patients presented with a classical cardiovascular risk profile. Preoperative hemoglobin, hematocrit and platelets were 14.5±2.0 g/dl, 42.8±4.7 %l, 255±55x10^3/µl. Only three patients required preoperative i.v. iron and erythropoietin therapy due to low hemoglobin levels (≤12 g/dl). INR (0.97±0.07) was normal in all patients. No blood transfusions occurred, while hemodynamic substitution was performed with Ringers's Lactate (873±367 ml), Voluven (700±388 ml) and indirect re-transfusion via the Cell Saver (474±101 ml). The mean duration of the procedure was 246±39 minutes, mean CPB-time 75±60 minutes, mean cross-clamp time 49±40 minutes and among patients who underwent the off-pump approach, no emergent conversion to CPB was necessary. Except for one episode of ventricular fibrillation in one patient which could be immediately terminated via defibrillation, no complications occurred postoperatively. No re-exploration for bleeding was necessary and all patients had a swift postoperative course. Mean postoperative ventilation time was 548±235 minutes, and except for two patients, all others were transferred from the ICU on the first postoperative day (mean length of ICU stay 25.9±12.2 hours).

The mean hemoglobin and hematocrit at the third postoperative day was 10.0±1.5 g/dl and 29.5±4.5% and the mean decrease in comparison to the preoperative levels was 31±8% and 31±7%. After a mean hospital stay of 7±1 days, the patients were discharged with mean hemoglobin of 10.6±1.2 g/dl and a hematocrit of 32.2±3.2%. In addition to this, it became apparent that the early postoperative decrease of hemoglobin and hematocrit levels was the lowest in patients who underwent an off-pump approach for myocardial revascularization when compared to all other procedures requiring CPB (25±9% vs. 33±6%; p=0.01 and 22±9% vs. 31±6%; p=0.04). Similarly, the decrease of platelets was significantly lower (20±12% vs. 43±14%; p=0.01) and did not drop below the normal range of 150–400 x 10^3/ml even after off-pump surgery. The mean follow-up time was 52±34 months and was completed in all patients (100%, n=16). Within this period, one patient died due to a non-cardiac reason (pneumonia). All other patients were alive, were in good health and had returned to normal life. None of them reported having any major adverse cardiac events (MACE) or any recurrent cardiac symptoms requiring redo surgery or a re-intervention.

These results demonstrated safety and feasibility of complex open-heart surgery in patients not accepting blood products and highlighted that Patient Blood Management leads to excellent clinical short- and long-term outcomes. Combined efforts in regard to preoperative hemoglobin optimization, effective intra-operative volume management as well was goal directed transfusions guided by ROTEM®, senior surgical staff and modern surgical techniques make this possible and permit complete avoidance of blood products.

Intra- and postoperative bleeding management can easily be performed by ROTEM® and allows for correcting coagulation factors such as fibrinogen, factor XIII and PBSB and avoidance of blood transfusion. In these cases, Patient Blood Management allowed major cardiac surgery without using any blood. The question which has to be raised is why Patient Blood Management is not offered to all patients as the standard of care.

2) Trauma

In a fourth study in trauma patients the question of the diagnosis of hyperfibrinolysis by ROTEM® was investigated as standard laboratory analysis do not provide adequate test within a reasonable time.[4]

Hyperfibrinolysis is a pathological state that occurs when the balance between fibrinolytic activators and its inhibitors are disturbed and is associated with significantly higher morbidity and mortality. Hyperfibrinolysis is commonly found in patients suffering from liver failure and during the an-hepatic period of liver transplantation; during brain injury and intracranial surgery; postpartum hemorrhage, during the cardiopulmonary bypass period; in a disturbed microcirculation as well as shock conditions; and in major trauma patients. However, the incidence of hyperfibrinolysis is still unknown, and its occurrence has only been estimated for patients with liver disease and major trauma patients in the range of 30% to 46% and 15% to 20%, respectively. One reason for the nescience regarding the incidence of hyperfibrinolysis may be that it is often underdiagnosed due to a lack of appropriate and real-time routine laboratory tests. In a two year period from April 2008 to April 2010, all emergency patients with hyperfibrinolysis were enrolled in this study. Hyperfibrinolysis patients were divided into two groups: traumatized and nontraumatized patients. The traumatized patients were matched with 24 polytrauma patients without hyperfibrinolysis. Data from the ROTEM® measurements, blood gas analysis, laboratory analysis, injury severity score, and 30-day mortality were collected. A total of thirty-five patients with hyperfibrinolysis could be identified (13 traumatized, 22 non-traumatized). Overall mortality for hyperfibrinolysis was 54%. Mortality in traumatized patients (77%±12%) was significantly higher than in non-traumatized (41%±10%; p=0.001, 95% CI 5%–67%) and polytrauma patients without hyperfibrinolysis (33%±10%; p=0.009, 95% CI 13%–74%). Hyperfibrinolysis was significantly (p=0.017) associated with mortality in trauma patients. In the blood gas analysis

representing the metabolic state, only pH (p=0.02) and potassium (p=0.01) were significantly lower in traumatized patients compared to the non-traumatized.

Mortality from hyperfibrinolysis was significantly higher in traumatized compared with non-traumatized patients furthermore hyperfibrinolysis can be used as an independent factor to predict mortality in trauma patients. Actually only ROTEM® provides real-time recognition of hyperfibrinolysis and allows early treatment.

3) The association with standard laboratory test

In a fifth study the important question regarding the association between standard laboratory tests, coagulation factor concentrations and ROTEM® in patients undergoing major surgery with hemorrhage was addressed.[5] In 45 patient's fibrinogen, factor VIII, factor XIII, INR, aPTT, thrombin time, hemoglobin, leukocytes and platelet count were simultaneously measured intra-operatively with ROTEM® (EXTEM, INTEM, FIBTEM, APTEM) measurements. ROTEM® parameters determined were: Clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF) and α-angle. Demographic and laboratory data were expressed as mean ± SD and median [range]; non parametric Spearman rank correlations and multiple linear regressions were performed; p-values ≤ 0.003 were considered significant.

Significant correlations ($p \leq 0.003$) were found for CFT, α-angle and MCF, in EXTEM, INTEM and APTEM with platelets, INR and fibrinogen. Factor VIII showed a strong correlation ($r \geq 0.7$ or $r \leq -0.7$; all $p \leq 0.003$) with MCF, CFT and α-angle of EXTEM, INTEM, MCF of FIBTEM excluding CT of EXTEM, INTEM, FIBTEM and strong significant correlation for α-angle APTEM and moderate for CFT and MCF APTEM. A significant moderate to strong correlation of factor XIII with MCF of EXTEM, INTEM, FIBTEM and APTEM was found. Hemoglobin was moderately correlated (r=0.3 to 0.7 or r=-0.3 to -0.7) with MCF in APTEM (p=0.003). A moderate to strong correlation of the standard coagulation tests with all ROTEM® parameters was found, in particular the CT. The aPTT correlated significantly moderate to strong with CT, CFT, α-angle and MCF of INTEM. However,

multiple linear regressions was not able to show an influence of INR on ROTEM® parameters except for APTEM-MCF. A significant impact of the aPTT on INTEM-CT was found. EXTEM, INTEM and APTEM are significantly influenced by fibrinogen and platelets. These results confirm the clinical assumption that EXTEM, INTEM and APTEM are associated with fibrinogen and platelets levels; INTEM-CT significantly to aPTT; and FIBTEM significantly to fibrinogen. Factor VIII showed a significant correlation with all ROTEM® parameters except CT of EXTEM, INTEM, FIBTEM and CFT and MCF of APTEM. This means that ROTEM can be partially used instead of standard laboratory measurements with the advantage that results are available within a much shorter time delay.

Conclusion

The presented research elucidates the important role of ROTEM® in monitoring coagulation, guiding goal-directed coagulation and transfusions treatment and its use in addition or in lieu of standard laboratory tests.

Furthermore ROTEM® is actually the only device able to detect hyperfibrinolysis in real time and therefore allowing its rapid detection and treatment. In addition, it is a predictor of mortality in traumatized patients. Further studies in this clinical setting are needed to evaluate the sensitivity of ROTEM® regarding the detection of hyperfibrinolysis, as it is possible that lower grades and local hyperfibrinolysis cannot be detected by the current technology. More studies on ROTEM® in special subgroups such as for example trauma, post-partum bleeding and liver transplantation are needed.

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